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CERTIFICATE

This certificate is issued in support of an application for Patent registration in a country outside New Zealand pursuant to the Patents Act 1953 and the Regulations thereunder.

I hereby certify that annexed is a true copy of the Provisional Specification as filed on 2 October 2003 with an application for Letters Patent number 528648 made by AgResearch Limited.

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PROVISIONAL SPECIFICATION

ALTERING ANIMAL WASTE COMPOSITION

I/WE AgResearch Limited, a New Zealand company duly incorporated pursuant to the Crown Research Institutes Act 1992 and having its Registered Office at 5th Floor Tower Block, Ruakura Research Centre, East Street, Hamilton, New Zealand,

do hereby declare this invention to be described in the following statement:

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ALTERING ANIMAL WASTE COMPOSITION

TECHNICAL FIELD

This invention relates to a method of altering the composition of animal waste.

BACKGROUND ART

One of the major environmental issues surrounding intensive farming situations is the release of nitrogen containing compounds into the environment.

Nitrogen is an important component in pastures for the growth and health of plants and soil microorganisms. The decay of organic matter such as from plant and animal wastes adds nitrogen to the soil largely in organic forms which plants are unable to use. Microorganisms present in the soil convert the organic forms of nitrogen to inorganic forms such as nitrate which can then be taken up by plant roots to generate new organic matter. This conversion of nitrogen is termed The Nitrogen Cycle.

Organic and inorganic forms of nitrogen may also be added to the soil through the addition of fertilisers to pasture.

Nitrogen containing compounds are a significant component in animal waste such as urine. Intensive farming practices such as dairying release a large quantity of urine-derived nitrogen to the soil, largely in the form of urea which is transformed rapidly into ammonium salts and then into nitrate by soil bacteria.

Large proportions of nitrogen are however lost from the soil, through a number of mechanisms, affecting the productivity of pasture and leading to environmental concerns.

Such mechanisms include denitrification, whereby soil bacteria convert nitrogen containing compounds in the soil to atmospheric nitrogen including nitrous oxide (a

greenhouse gas); volatilisation, wherein ammonium salts can volatilise into ammonia which also join the atmosphere; runoff, which carries nitrogen from the soil into rivers and streams; and leaching wherein nitrates move through the soil into groundwater.

Urea, applied to the soil either as fertiliser or animal waste, is typically transformed rapidly into ammonium salts and then into nitrate by soil bacteria. Nitrate is highly mobile and moves easily with water through the soil, affecting groundwater and water quality.

To attempt to minimise the loss of nitrogen from the soil, a number of different methods have been developed.

These methods include feeding of low protein forages to animals to decrease the amount of nitrogen cycling and use of feed pads to collect and evenly spread excreta.

Other research groups have been developing new fertiliser compositions containing urease or nitrification inhibitors to slow the conversion of urea to ammonium salts, or from ammonium salts to nitrate respectively, enhancing the residence time of nitrogen in the soil and thus reducing the amount of nitrogen lost to the atmosphere or leached from the soil as nitrate.

Nitrification inhibitors may be applied directly to soil to reduce nitrification reactions. When a cow urinates on the treated ground, the inhibitors slow the conversion of ammonium to nitrate in the urine soaked patch.

However, the application of inhibitors over large areas of ground is problematic. Complete contact with nitrogen sources prone to high nitrate production (eg surface soil nitrogen after cultivation or urine-affected zones in soil) is uncertain. Further, the inhibitors may break down in the environment before being of use, or

leach through to ground water.

WO 02/19809 describes a dispensing device located about the tail of a dairy cow and configured to release urease and/or nitrification inhibitors as the cow raises its tail whilst urinating.

WO 02/19809 overcomes some of the practical difficulties in delivering inhibitors into the urine stream and therefore to the zone of soil affected by the urine. However, WO 02/19809 in turn presents practical difficulties of its own as such devices require regular maintenance to ensure they contain sufficient inhibitors and have not been knocked or rubbed off, or become fouled or otherwise blocked.

Methods and compositions for the sustained release of active agents in to the bladder have previously before been described, particularly in the treatment of bladder cancer in humans.

US 6,306,422 describes the use of urease inhibitors contained within a pH-sensitive polymer matrix which can be coated onto objects such as catheters.

A common problem with catheterised patients is the infection of the urinary tract with urease-producing bacteria. The conversion of urea to ammonium by the bacteria results in an increase in pH of the urine, which in turn causes the pH-sensitive polymer to swell and release antibiotics or urease inhibitors to treat the infection.

In most situations, ureases are not present in the bladder of an animal and thus the inhibitors remain trapped within the polymer matrix. Accordingly, this composition is not particularly useful for affecting the conversion of urea to ammonium in the absence of infection.

US 6,524,608 describes compositions that have a lower specific gravity than urine, which when infused into the bladder effectively float and are not expelled along

with the urine. Instead, the composition is slowly bio-eroded to provide the sustained release of drugs.

Other devices such as that described by US 6,171,298 utilise collapsible balloons placed within the bladder, which can release substances over time.

However, such compositions and devices are concerned with the delivery of active substances internally to treat a range of medical conditions, and are not directed to using the urine as a delivery mechanism for active substances to the external environment.

All references, including any patents or patent applications cited in this specification are hereby incorporated by reference. No admission is made that any reference constitutes prior art. The discussion of the references states what their authors assert, and the applicants reserve the right to challenge the accuracy and pertinency of the cited documents. It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of these documents form part of the common general knowledge in the art, in New Zealand or in any other country.

It is acknowledged that the term 'comprise' may, under varying jurisdictions, be attributed with either an exclusive or an inclusive meaning. For the purpose of this specification, and unless otherwise noted, the term 'comprise' shall have an inclusive meaning - i.e. that it will be taken to mean an inclusion of not only the listed components it directly references, but also other non-specified components or elements. This rationale will also be used when the term 'comprised' or 'comprising' is used in relation to one or more steps in a method or process.

It is an object of the present invention to address the foregoing problems or at least to provide the public with a useful choice.

Further aspects and advantages of the present invention will become apparent from the ensuing description which is given by way of example only.

DISCLOSURE OF INVENTION

According to one aspect of the present invention there is provided a method of altering the composition of animal waste,

characterised by the step of:

introducing to an animal a treatment substance that can directly or indirectly affect the conversion of nitrogen containing compounds in animal waste, once the waste has been excreted from the animal.

According to another aspect of the present invention there is provided a device for altering the composition of animal waste,

characterised in that

the device is configured to introduce to an animal a treatment substance that can directly or indirectly affect the conversion of nitrogen containing compounds in animal waste, once the waste is excreted from the animal.

The term "animal waste" should be taken to mean any waste products excreted by the animal such as faeces and urine.

In preferred embodiments of the present invention the animal waste is urine. For ease of reference throughout this specification, the terms "animal waste" and "urine" will be referred to as urine. However, this should not be seen as a limitation on the present invention in any way.

In preferred embodiments of the present invention the animal will be a farm animal, and more preferably a dairy animal such as a cow. Once again, this should not be

seen as a limitation as it is anticipated the present invention could be used on other intensively farmed animals such as beef cattle, sheep, goats and so forth, as well as other animal species, including humans.

The term "treatment substance" should be taken to mean any substance capable of directly or indirectly affecting the conversion of nitrogen containing compounds.

In preferred embodiments of the present invention the treatment substance contains at least one active compound such as a urease or nitrification inhibitor which affects the conversion of urea to ammonium, and ammonium to nitrate respectively.

In other preferred embodiments the active compound may enhance the immobilisation of high levels of inorganic nitrogen into organic nitrogen and permit sustained slower release of nitrogen, thereby enabling greater likelihood of overall plant nitrogen recovery and reducing the high inorganic component prone to loss. For example, it is anticipated that tannin, or another complex carbon source may be used to enhance the immobilisation of nitrogen. It is also anticipated a number of other active compounds could also be used.

For ease of reference, the term "treatment substance" will herein be referred to as a nitrogen process modifier.

The term "nitrogen containing compound" should be taken to mean any compound which contains nitrogen as part of its chemical structure.

In preferred embodiments the nitrogen containing compounds include those found in urine, or produced during the conversion of urine such as urea, ammonium, ammonia and nitrate as well as nitrogen gases including nitrous oxides, and soluble organic forms.

In preferred embodiments of the present invention the animal waste is used as a

transfer mechanism for the introduction of treatment substances which affect the conversion of nitrogen containing compounds in the environment.

Delivering the nitrogen process modifiers along with the animal waste means there is no delay in modifying the conversion of nitrogen containing compounds. Further, this ensures the modifiers are only delivered to the portion of pasture/soil on which the cow urinates, eliminating the need to apply the modifiers over a large area of pasture.

Further, introducing the modifiers internally to the animal eliminates the need for attaching devices to the exterior of the animal, which require regular maintenance to ensure they contain sufficient modifiers, have not been damaged, or have not become fouled or otherwise blocked.

The modifiers of the present invention may be introduced to the animal by a number of mechanisms.

In preferred embodiments of the present invention the modifiers may be introduced to the animal from a slow release device inserted into an animal's bladder by a farmer or veterinarian.

Preferably, the device will comprise a solid, preformed stable matrix wherein the introduction of the modifiers is by diffusion of those substances from the matrix over a period of time.

For example, the device may be made of silicone matrix which is impregnated with the appropriate modifiers.

The modifiers may be delivered through dissolution processes from the matrix or by the placement of appropriate modifiers within the inner core of the device under various delivery systems.

In preferred embodiments the device may be bio-erodeable, obviating the necessity for the device to subsequently be removed from the animal after treatment, which would require significant time and effort.

Other preferred embodiments of the present invention may utilise lipid-based delivery vehicles such as liposome-coated compositions, or other slow release matrices known in the art such as bio-erodeable wax coatings, synthetic polymers, cross-linked cellulosic compounds and so forth. For example, in some embodiments weakly acidic or basic co-monomers may be used which slowly release the modifiers during contact with urine.

The sustained release of modifiers over time into an animal's bladder allows the modifiers to be excreted from the animal as a component of the urine, thus directly or indirectly affecting the conversion of urea to ammonium salts and ammonium salts to nitrate by soil bacteria, or altering immobilisation/mineralization of these compounds to increase overall recovery by plants.

In other preferred embodiments the modifiers may be introduced to the animal through the digestive system of the animal.

For example, the delivery device may be in the form of a sustained slow release device such as a rumenal bolus, administered orally to an animal.

As understood by a person skilled in the art, a bolus is typically in the form of an elongate cylinder designed to slowly dissolve in the rumen of an animal.

One advantage of having sustained released devices is that the amount of modifiers released can be accurately known. This makes the treatment and the analysis of the effects of the treatment of the animal much more precise than previously.

The bolus will preferably be comprised of a solid matrix, coated with an impervious

material having an opening through which the modifiers can be released, or a bio-erodeable coating which releases the modifiers as they are exposed.

A wide variety of boluses and other delivery mechanisms are well known in the art and it is anticipated these technologies could readily be adapted by a skilled addressee for use in the present invention.

Other delivery mechanisms may also be used for the application of the modifiers to the animal. These may include incorporating the modifiers in animal feed or by other traditional delivery mechanisms such as drenches or injections.

When delivering the modifiers via the digestive system, it is essential to ensure that modifiers maintain their activity and are not denatured or inactivated through the passage of the animal digestive system.

In some embodiments, the bolus and/or modifiers may be encapsulated to provide protection against denaturation and subsequent absorption in the rumen or intestine.

Other embodiments of the delivery device may utilise an electronic device as powered by an electrochemical cell, to provide sufficient modifiers over the treatment period. Such devices may be inserted into an animal's body cavity and be removed following the treatment period.

While such devices could be inserted into an animal's bladder, these will likely require surgical removal and thus considerable time and labour. Devices may also be located in the rumen of an animal, which may remain in-situ or may be excreted after a period of time.

Methods and compositions for the sustained release of active agents in to the bladder have previously before been described, particularly in the treatment of bladder cancer in humans. It is anticipated that a skilled addressee would readily

be able to adapt these methods for use in the present invention.

For example, in some embodiments there may be provided a mechanism which can be anchored to a device for later retrieval after the treatment period.

Such a mechanism may be a collapsible slow release membrane balloon. The balloon can be inserted into the bladder through a urethral catheter when in collapsed form. The balloon can then be injected or infused via the catheter with modifiers. Once the substances have been delivered to the bladder, the balloon can then be withdrawn in its collapsed form through the urethra.

The balloon may deliver the substances through for example, dissolution and therefore will collapse naturally. In other embodiments, the balloon may be punctured to collapse it before it is withdrawn through the urethra.

To enable accurate placement of the collapsible balloon within the bladder, the device may be used to act as an anchor for the balloon component of the device, or alternatively the balloon may effectively "float" in the bladder. One example of such a device is described by US 6,171,298.

Other compositions are known in the art such as those described in US 6,524,608 have a lower specific gravity than urine, and which when infused or inserted into the bladder effectively float and are not expelled along with the urine. Instead, the composition is slowly bio-eroded to provide the sustained release of drugs.

It is anticipated that the use of nitrogen process modifiers will be most effective over a seasonal time period such as from mid-autumn to late-winter, a period of approximately three to four months. As such it will be desirable to have a composition or device that slowly released modifiers over this time period.

During this time period, nitrogen is most prone to loss by processes of leaching and/or denitrification/nitrous oxide emission.

However, this should not be seen as a limitation for in other embodiments the modifiers may be delivered over a shorter time period, with a number of treatments administered to the animal as required.

In one preferred embodiment of the present invention, nitrogen process modifiers such as urease inhibitors may be used to slow the conversion of urea to ammonium.

It is desirable to use inhibitors that can be used in small amounts, and which are non-toxic to the animal.

A number of urease inhibitors are known in the art which may find use in the present invention. For example, N-(n-butyl) thiophosphoric triamide (nBTPT) is used commercially under the trade name Agrotain™ and has been used with urea fertiliser to reduce ammonia volatilisation.

Acetohydroxamic acid has been used to control nitrogen metabolism in animals. Further, it should be understood that other substitutes or alternative urease inhibitors might also be used in the present invention.

In other preferred embodiments, nitrification inhibitors may also be used, alone or combination with urease inhibitors. For example, a nitrification inhibitor suitable is 3,4-dimethylpyrazole phosphate (DMPP), which has been shown to inhibit nitrification of fertiliser N when applied at relatively low rates and is non-toxic.

Another nitrification inhibitor which may find use is dicyandiamide (DCD).

The device may also preferably deliver other beneficial compounds which function to improve or condition microorganisms already present in the soil, allowing them to better bind the excess nitrogen in urine excreted by animals.

For example, tannins or other complex carbon sources can be used to enhance

the immobilisation of nitrogen into soil organic nitrogen, for a more sustained release.

According to another aspect of the present invention there is provided a pharmaceutical composition for introduction to an animal to alter the composition of animal waste,

characterised in that the pharmaceutical composition includes

a treatment substance for directly or indirectly affecting the conversion of nitrogen containing compounds in animal waste, and

material to ensure the conversion is affected once the animal waste is excreted from the animal.

According to a further aspect of the present invention there is provided a method for the manufacture of a pharmaceutical composition containing a treatment substance for altering the composition of animal waste, by directly or indirectly affecting the conversion of nitrogen containing compounds in animal waste once the animal waste is excreted from the animal.

The term "material" should be taken to mean any material which ensures the conversion of the nitrogen containing compounds is affected once the animal waste is excreted from the animal and may include biodegradable and/or bio-erodeable matrices known in the art, such as lipid-based coatings, wax coatings, polymer matrices.

As material breaks down in the environment, the modifiers are released and slow or alter the conversion of nitrogen containing compounds in the soil.

The function of the modifiers includes slowing the rate of transformation of urea to nitrate, through the inhibition of ureases produced by bacteria in the soil, by

slowing the nitrification of ammonia to nitrate, enhancing the immobilisation of inorganic nitrogen into soil organic forms.

Inhibiting or modifying the conversion of nitrogen containing compounds allows more time for the nitrogen excreted in animal waste to be absorbed by plants, before being lost by soil processes such as leaching from the soil as nitrate. This will not only improve soil fertility, but also reduce the level of nitrates entering groundwater and affecting both water quality and drinking water supplies.

It will also likely reduce the levels of nitrous oxide released to the environment and thus reducing levels of greenhouse gases emitted from intensive farming operations.

Having a device which bio-erodes in the bladder allows only a certain amount of modifier to be released at any one time, dependent on the volume of urine excreted by the animal and as such reduces the wastage of modifiers.

BEST MODES FOR CARRYING OUT THE INVENTION

As defined above, in its primary aspect, the present invention is directed to a novel method of altering the composition of animal waste by introducing to an animal a treatment substance that affects the conversion of nitrogen containing compounds in animal waste, once the waste has been excreted from the animal.

The invention is based upon the inventor's investigation into the delivery of nitrogen process modifiers and the modification of nitrogen containing compounds in animal waste.

One preferred embodiment of the present invention consists of a bolus administered orally to grazing animals with targeted delivery to the animal waste,

and urine in particular. In preferred embodiments the bolus is in the form of a slow release bolus which is inserted into the rumen and which releases nitrogen transformation modifiers over a sustained period of up to four months.

A generic composition of the bolus is as follows,

i) a core comprising a substantially homogeneous mixture of:

a) a water insoluble physiologically acceptable binder comprising wax, fat, oil, fatty acid, fatty acid ester, fatty acid amide, fatty acid alcohol or the like organic compound having a melting point above 50ºC;

b) a physiologically acceptable solubilising agent, such as polyethylene glycol stearate or the sodium salt of a long-chain fatty acid.

c) at least one nitrogen transformation modifier

d) where required, a physiologically acceptable inert densifier of sufficient density and in sufficient quantities to give the bolus a minimum density of 1.5g/cm^3; and

ii) a coating of a physiologically acceptable material over substantially all of the surface of the core but leaving exposed a core portion whereby in use liquid in the rumen will dissolve said core allowing release of the nitrogen transformation modifier into the rumen.

One preferred embodiment of the bolus may include a nitrogen transformation modifier in the form of nitrification inhibitor such as DMPP up to 100g with a binding agent such as glycerol monostearate.

In another preferred embodiment of the present invention the nitrogen process modifiers may be delivered from a slow release composition inserted into the bladder of animals. In these embodiments, a nitrogen inhibitor such as DMPP is

incorporated with a minimal amount of a suitable carrier into a structure such as a flexible filamentous extrusion which is inserted into the bladder using a catheter.

To retain the composition in the bladder, the composition preferably has a specific gravity less than or equal to that of urine, which is normally about 1.005gm/ml to 1.033gm/ml at 25°C. This allows the device to be neutrally buoyant or float in the urine of the bladder minimising the blockage of the urethra.

The composition could contain multiple constituents, a nitrification inhibitor such as DMPP, a urease inhibitor such as NBPT and/or an N-transformation modifier such as a tannin.

Aspects of the present invention have been described by way of example only and it should be appreciated that modifications and additions may be made thereto without departing from the scope thereof.

AGRESEARCH LIMITED

by its Attorneys

JAMES & WELLS

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